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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,567	09/04/2003	Futoshi Okada	Furuya Case 1407	6434

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EXAMINER	
KOSSON, ROSANNE	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 09/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/655,567	OKADA ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on August 25, 2004 has been received and entered. The Declaration under 37 CFR 1.132 filed on August 25, 2004 has been received. The text of those sections of Title 35, U.S. code, not included in this action can be found in a prior office action.

Claims 1 and 4-15 are pending and are examined on the merits.

Claim Rejections - 35 USC § 112

Claims 1 and 4-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a tumor with melon SOD combined with gliadin, does not reasonably provide enablement for a method of preventing a tumor by the administration of SOD combined with gliadin. The specification discloses administering SOD combined with gliadin to mice with tumors, to a human with colon cancer, and to a human who had had a cancerous prostate removed. Shrinkage of the tumors was measured, and the subjects were examined for reappearance of tumors. Thus, Applicants have not demonstrated administration of an SOD formulation to prevent tumors. Prevention of tumors in a subject may be asserted in any case where an SOD formulation is administered to a normal subject, and the subject has not yet developed tumors (or prostate or colon cancer). Therefore, a holding of non-enablement is clearly required.

All of Applicants' arguments regarding this rejection for the scope of enablement have been considered but are not persuasive of error. The experimental data in the

application show that gliadin-coated SOD is effective in reducing the size of tumors (Figure 1) and in inhibiting the growth of existing tumors (first patient case). The data also show that this composition is effective in decreasing the incidence of tumors in the lungs when tumor-producing cells are injected into mice. Applicants note on p. 3 of the specification that the QR-32 tumor cells used in the experiments become malignant when grown in the presence of a gelatin sponge. Cell lines may be established from the tumors, and the host inflammatory cells removed, but Applicants have not provided evidence that these QR-32 cells have reverted to a benign state. Further, the matter of preventing the malignant transformation of benign tumor cells does not appear in the claims. Thus, Applicants have demonstrated that gliadin-coated SOD can effectively treat tumors or inhibit the growth of tumor cells. But, the data do not support that tumors in a subject can be prevented by administering gliadin-coated SOD. Accordingly, the rejection of record must be maintained.

In view of Applicants' amendments to the claims, the rejections under 35 U.S.C. 112, second paragraph, are moot and are withdrawn.

Claim Rejections - 35 USC § 102

In view of Applicants' amendments to the claims, the rejections under 35 U.S.C. 102(b) are moot and are withdrawn.

Claim Rejections - 35 USC § 103

Claims 1 and 4-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murcia et al. (J Food Prot 64(12):2037-2046, 2001) in view of Postaire et al. (U.S. 6,045,809) and Ginoux (U.S. 5,616,323). Murcia discloses that melon has significant SOD activity, as shown by its antioxidant and free radical ($OH^{\cdot}$) scavenging activity (see pp. 2039-2043, Results and Discussion and Tables 1-3). Postaire discloses a composition comprising superoxide dismutase (SOD) and gliadin, which stabilizes this enzyme at acidic pH and provides a controlled release formulation (see column 3, lines 1-11). It would be obvious to one of ordinary skill in the art to formulate the SOD-containing composition of Murcia (melon pulp) as the gliadin film-coated SOD-containing composition of Postaire because the formulation of Postaire is adapted for oral administration, good bioavailability and therapeutic efficacy (see column 1, lines 6-9). Further, the skilled artisan would be motivated to use the SOD-containing composition of Murcia because melons are a readily available source possessing potent SOD activity. Ginoux discloses administering SOD-containing extracts from melon to treat cancer (see column 1, lines 6-10 and 59-65, column 2, lines 21-24, and column 5, lines 13-29). Thus, it would be obvious to one of ordinary skill in the art to use a gliadin-coated SOD-containing composition to treat cancer, rather than uncoated SOD-containing melon pulp, because, as recited in Postaire, the gliadin-coated composition is more acid-stable and longer acting. As asserted in Ginoux, the gliadin-coated SOD-containing composition would be especially useful in the treatment of cancers. A holding of obviousness is therefore required.

All of Applicants' arguments regarding this rejection for obviousness have been considered but are not persuasive of error. Applicants assert that their gliadin-coated SOD (SOD-G) functions by a different mechanism than uncoated SOD. This point has been noted, but shows that SOD can inhibit the growth of tumor cells by more than one mechanism. The mechanism of action is not a limitation in the claims. Applicants also assert (see p. 8 of the Response) that SOD-G inhibited tumor growth and malignant progression. As discussed above, Applicants have demonstrated inhibition of tumor growth by SOD-G, as well as inhibition of metastasis, as recited in claim 8. But, as discussed above, Applicants have not demonstrated inhibition of malignant progression by SOD-G, i.e., inhibition of the conversion from the benign state to the malignant state, and inhibiting this conversion is also not a limitation recited in the claims.

Regarding the references submitted with the Response, Huber (reference 1) discloses that bovine Cu-Zn SOD is a potent anti-inflammatory. Kong et al. (reference 4) discloses that SOD has been found to decrease the efficacy of anti-tumor therapies that depend on free radical generation for their action. Kunimaka et al. (reference 5) discloses that increased expression (not pharmaceutical administration) of Mn-SOD diminishes the cytotoxic effect of several anti-cancer therapies, such as certain chemotherapies, radiation and hyperthermia, and visa versa. These references are not germane to the issue of obviousness. Huber deals with anti-inflammatory properties, not anti-cancer properties, of an SOD. The findings of Kong are not surprising. If an anti-cancer drug works via a mechanism in which free radicals are generated, one would expect that a free radical scavenger would inhibit the action of the drug.

Kunimaka deals with cells whose expression of Mn-SOD is increased or decreased. These cells may have been genetically manipulated for increased expression, that is, transfected with a Mn-SOD gene or a gene that enhances the expression of Mn-SOD, or the cells may have been treated with a compound that enhances Mn-SOD expression. Decreased expression was achieved by treatment with Mn-SOD anti-sense RNA. In any case, such cells are in a different state than cells that have been contacted with an SOD for treatment, particularly if the cells are from a mammal and the SOD is from a melon. If cells that over-express or under-express Mn-SOD have a different response to various cancer treatments than cells that express normal levels of Mn-SOD, this result may be useful. But it not surprising, nor is it particularly relevant to the claimed invention.

Applicants also argue that "treated" SOD comprises ethanol, methanol and prolamines and is, therefore, not the same as SOD extracted from melons. But, as "treated SOD" is not excluded from the amended claims, this argument is not directed to the breadth of the subject matter encompassed by the claims. The cited art still encompasses the SOD recited in the claims.

Concerning the references cited in the rejection of the claims, in response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants discuss the SOD composition of Ginoux and that it would not be effective for treating

tumors other than gastrointestinal tumors, but the rejection is that SOD-G is disclosed by Postaire and Ginoux discloses administering SOD (melon SOD) as an anti-cancer therapy. Because SOD-G is a more stable formulation with increased bioavailability, as disclosed by Postaire, it would have been obvious to one of ordinary skill in the art to substitute the SOD-G of Postaire for the SOD of Ginoux in treating cancer, because of the advantages disclosed by Postaire. The teachings of Murcia complement the disclosure of Ginoux that melon pulp has anti-cancer activity due to its antioxidant and radical scavenging properties. Applicants' comment that in Murcia superoxide dismutase activity was not measured is noted. But, although not specifically disclosed, the presence of SOD in melon pulp is suggested, and verified by Ginoux, which discloses that melon pulp has anti-cancer activity. Applicants also assert that because Postaire does not disclose using SOD-G to treat cancerous tumors, there is no motivation to combine the cited references. The motivation to use an extract of melon pulp as an anti-cancer treatment comes from Ginoux, while Postaire provides an improved formulation. Murcia recommends using melon pulp to treat cancer because melon pulp, as a mixture of oxygen-derived radical scavengers, can fight cancer in several different ways. Therefore, the rejection of record must be maintained.

The Declaration under 37 CFR 1.132, submitted unsigned, technically cannot be considered. To the extent that it demonstrates that Applicant's composition of gliadin-coated SOD (SOD-G) produces elevated levels of SOD in various tissues and blood, compared to SOD alone, gliadin alone or a control, the Declaration is insufficient to

overcome the rejection of claims 1 and 4-15 based upon the arguments as set forth in the last Office action, because there is no indication that the data presented therein were obtained using mice with any type of tumor or cancer. It appears that normal mice were used. The data show that when Applicants' SOD-G was orally administered to mice, various tissues and blood contained higher levels of SOD than when uncoated SOD, gliadin alone or a control substance was administered. These data have no relationship to cancer or tumors. Further, as discussed above, Postaire discloses Applicant's SOD-G and that this composition has improved bioavailability because of its improved stability upon passage through the GI tract and slow-release formulation into the body's tissues and circulation. Thus, one would expect that mice given SOD-G would have higher tissue and blood levels of SOD compared to mice given uncoated SOD or mice not given SOD. Accordingly, Applicants' data are quite an expected result, not an expected result. The Declaration does not serve to overcome the rejection of the claims on the grounds of obviousness.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, with alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rosanne Kosson
Examiner
Art Unit 1651

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2004-09-21